Neuroimaging and Other Neurodiagnostic Tests in Neonatal Encephalopathy

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KEYWORDS

• Hypoxic-ischemic encephalopathy • Birth asphyxia • MRI • MR spectroscopy
• Amplitude integrated EEG • Near-infrared spectroscopy

KEY POINTS

- Neonatal hypoxic-ischemic brain injury is associated with a high rate of death and disability despite the introduction of therapeutic hypothermia to clinical practice.
- Hypoxic-ischemic brain injury evolves over days and weeks, and interpreting magnetic resonance (MR) scans of infants with suspected birth asphyxia should take this concept of progression into account in order to avoid underestimating the extent of brain injury.
- Therapeutic hypothermia affects MRI, amplitude-integrated electroencephalogram, and near-infrared spectroscopy findings but should not impact the overall predictive values of these tests.
- Amplitude-integrated electroencephalogram and near-infrared spectroscopy are noninvasive tools that can help monitor brain functions at the bedside and predict long-term outcomes.
- Advanced MR techniques are promising in that they can help us better understand the pathophysiology of brain injury and assess its progression, in addition to fine-tuning clinicians' ability to predict outcomes.

NEUROIMAGING

The prediction of long-term outcomes in infants with neonatal encephalopathy is of great importance to families and clinicians, whether this information is used to pursue comfort care or to justify more invasive interventions. In addition, stratification of these infants may allow for identification of infants who will benefit from further

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neuroprotective therapies, some of which are currently being tested (eg, erythropoietin and stem cells). This review addresses the role of neuroimaging, amplitude-integrated electroencephalography (aEEG), and near-infrared spectroscopy (NIRS) for neurodevelopmental prognostication in term newborns with encephalopathy. This review also discusses the effect of therapeutic hypothermia on the predictive values of these tests.

Sensitivity means the ability of a test to correctly classify an individual as having a disease, in this case the ability of an abnormal MRI/aEEG/NIRS to classify an infant as having later disability. Specificity refers to the ability of a test to correctly classify a person as disease free, in this case the ability of normal MRI, aEEG, or NIRS to predict that an infant will *not* die or have severe disability. Unlike sensitivity and specificity, predictive values depend on the prevalence of the disease (in this case, abnormal neurologic outcome) in the population. Positive predictive value (PPV) is the percentage of patients with a positive test who actually have the disease, in this case the percentage of all infants with death or disability who had an abnormal MRI/aEEG/NIRS in the neonatal period. Negative predictive value (NPV) is the percentage of patients with a negative test who do not have the disease or the percentage of all infants with a good/normal outcome who had a normal MRI/aEEG/NIRS in the neonatal period.

MRI

With technology advances, the capacity to safely repeat brain imaging in critically ill infants has enabled studies confirming the clinical and experimental observations that neonatal brain injury evolves over days and weeks.[1] With the development of magnetic resonance (MR)-compatible incubators and monitoring equipment, MRI is now the modality of choice, although head ultrasound and computed tomography (CT) still have a role to play in specific circumstances. Despite its ability to detect the predominant patterns of brain injury after birth asphyxia, sensitivity and specificity of CT for injury are significantly lower than MRI[2]; there are important concerns of radiation exposure with its routine use.[3] Head ultrasound is often normal even in cases of severe birth asphyxia but can be used to rule out antenatal injury and intracranial hemorrhage. Imaging infants with birth asphyxia is important to confirm the diagnosis and exclude other causes of neonatal encephalopathy, such as metabolic disorders or neonatal stroke. Of note, MRI with diffusion-weighted imaging (DWI) seems to be the most sensitive imaging method to detect abnormalities associated with other causes of neonatal encephalopathy, such as cerebral dysgenesis, infections, stroke, and metabolic disorders. Imaging can also guide clinical decision-making and counsel families. The standard neonatal brain MRI protocol includes conventional anatomic sequences (T1- and T2-weighted imaging) and DWI. Brain imaging has revealed patterns of brain injury following a hypoxic-ischemic insult that are unique to the immature brain and that depend on the age at which it occurs and the severity and duration of the insult (**Fig. 1**).[4,5] These clinical investigations have confirmed the prolonged temporal evolution of brain injury that was initially revealed by neonatal animal models. This time course suggests a therapeutic window for interventions that could be instituted hours or days after the hypoxic-ischemic insult.[1]

In order to confirm the diagnosis of hypoxic-ischemic brain injury and determine the extent of injury, MRI and DWI are optimally acquired between 3 and 5 days of life in term newborns with encephalopathy.[6–8] In newborns treated with hypothermia, the *optimal* timing of MRI is unclear and will require further investigation.[9] In a neonatal primate model of brain injury, the distribution of injury is associated with the duration and severity of ischemia. Although acute and profound asphyxia produces injury in the basal ganglia and thalamus, prolonged and partial asphyxia causes diffuse injury in